Methods for the screening and diagnosis of gestational diabetes mellitus between 24 and 28 weeks of pregnancy

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Summary

The aim of this review is to provide answers to the question “How does one screen for and diagnose gestational diabetes mellitus (GDM) between 24 and 28 weeks gestation?” Two methods are currently widely used: a one-step approach (the 75g-Oral Glucose Tolerance Test, OGTT) and a two-step approach (the 50g Glucose Challenge Test, GCT, followed by 100g-OGTT). A review of the literature showed that both methods had good reproducibility (around 80%), whilst neither required preliminary diet changes. The data of the Hyperglycaemia Adverse Pregnancy Outcomes (HAPO) study on materno-foetal morbidity provided consistent support in favour of the 75g-OGTT. In addition, this one-step method presents several advantages over the two-step method, i.e. it provides a faster diagnosis time, better tolerance and it is easier to remember. We therefore recommend a 75g-OGTT including three measures of the glycaemia at times 0, 1 and 2 hours for the diagnosis of GDM between 24-28 weeks of pregnancy. A discussion of alternative methods revealed that measuring Fasting Glycaemia (FG) between 24 and 28 weeks of pregnancy was unsuitable, and that measuring HbA1c, fructosamine, glycosuria, or random and postprandial plasma glucose was not advisable. This is based on the fact that too few studies have evaluated these methods, and that the studies usually involved heterogeneous populations in varying numbers, using differing criteria and sensitivity values. However, HbA1c measurements may prove useful in detecting pre-pregnancy diabetes mellitus.

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Keywords: gestational diabetes mellitus, screening, oral glucose tolerance test, fasting glucose, glycated haemoglobin, review

Résumé

Méthodes du dépistage et du diagnostic du diabète gestationnel entre 24 et 28 semaines d’aménorrhée

Cette revue a pour objectif de répondre à la question « comment dépister le diabète gestationnel (DG) entre 24 et 28 semaines d’aménorrhée (SA) ? ». Il existe actuellement deux méthodes diagnostiques, en un temps (HGPO-75 g) et en deux temps (50 g suivi HGPO-100 g). L’analyse de la littérature montre que chacune des méthodes a une bonne reproductibilité de l’ordre de 80%, sans nécessiter de modifications diététiques préalables. L’étude HAPO apporte des données solides sur la morbidité materno-fœtale en rapport avec les glycéémies de l’HGPO-75 g. De plus, l’HGPO-75 g a plusieurs avantages par rapport au dépistage en 2 temps : réduction du délai de la prise en charge diagnostique, meilleure tolérance, mémorisation plus simple. Les experts recommandent pour le dépistage et le diagnostic du DG, une HGPO-75 g avec mesure des glycéémies à 0, 1 et 2 h. Les différentes autres méthodes sont discutées. La mesure de la glycémie à jeun entre 24 et 28 SA n’est pas une méthode pertinente. Aucune des autres méthodes (HbA1c, fructosamine, glycosurie, glycémie au hasard et postprandiale) n’est recommandée. En effet, les études qui ont évalué ces méthodes sont peu nombreuses, réalisées dans des populations hétérogènes, avec des critères variables, sur des effectifs variables, et avec des valeurs de sensibilité variables. Seule la mesure de l’HbA1c pourrait être utile pour dépister un diabète prégestationnel.

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Mots clés : diabète gestationnel, dépistage, hgpo, glycémie à jeun, HbA1c, revue

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1. Introduction

The 75g-Oral Glucose Tolerance Test (OGTT), also known as Provoked Oral Hyperglycaemia (POHG), used to be the method of reference to diagnose sugar diabetes in the general population. Nowadays, the recommended test involves measuring fasting plasma glucose [1]. There is no universal reference diagnostic for pregnant women. Instead, two diagnostic methods are currently available: a one-step method (the 75g-OGTT), and a two-step method (the 50g followed by 100g-OGTT). Historical work by O’Sullivan and Mahan in 1964, developed the two-step method and the first diagnostic criteria for Gestational Diabetes Mellitus (GDM), based on the risk of evolution into type 2 diabetes [2]. While these criteria are robust from an epidemiological point of view, they were not developed on the basis of short-term maternal-child morbidity. This explains why they have since been regularly revisited, in an attempt to take better account of maternal-child morbidity and mortality [3, 4]. In addition, the complexity of the two-step method has led various learned societies to recommend alternative methods.

The International Association of Diabetic Pregnancy Study Groups (IADPSG) was created in 1998 to facilitate international collaboration. This group brings together 220 experts form 40 countries, and numerous learned societies and reference organisations, including the ACOG (American College of Obstetricians and Gynecologists), WHO (World Health Organization), ADA (American Diabetes Association), EASD (European Association for the Study of Diabetes), IADP (Japanese Association for Diabetes and Pregnancy), ADPS (Australasian Diabetes in Pregnancy Society), DPSI (Diabetes in Pregnancy Society India), CSIGDP (Canadian Special Interest Group for Diabetes and pregnancy). IADPSG’s main objectives were to develop an international approach to research on gestational diabetes mellitus, and to foster the emergence of universal recommendations. The group met in June 2008 to analyse data from the HAPO study, and to submit a report – endorsed by specialists of diabetes, obstetricians and various organisations –, to serve as a basis for the diagnosis and classification of GDM [5].

3. Material and methods

3.1. Sources of information

3.1.1. PubMed (Medline) database queries

The following search terms were systematically used in conjunction with “gestational diabetes mellitus”: screening methods, diagnosis, recommendations, consensus conference, oral hyperglycaemia, fasting glycaemia, postprandial glycaemia, capillary glycaemia, HbA1c, fructosamine, glycosuria, random glycaemia measurements, dietetics.

3.1.2. Other sources

Data on GDM from the Cochrane database.
Analysis of articles referenced over the last 10 years as systematic literature reviews, meta-analyses, recommendations and consensus conferences.
Internet searches using the Google search engine

4. Selection criteria for the articles

All recommendations and consensus conference articles over the last 10 years were considered. Articles were selected on the basis of their title, abstract and being published either in French or in English. Analysed articles included recommendations, reviews, original articles or cohort studies. The populations studied included pregnant women, with or without GDM. The original studies we analysed were comparative, and cohort studies were either prospective or retrospective. Recommendation articles, comparative or controlled, cross-over, randomized studies were used for the section on strategic diagnosis. Comparative studies were used for the sections on sensitivity/specificity. Repeated-measure prospective studies were used for the sections on reproducibility.

5. Historical recommendations

Diagnosis of gestational diabetes mellitus is based on OGTT. The one-step strategy is based on a single OGTT involving two measurements of venous glycaemia 0 and 2h after ingesting 75g of glucose. The two-step strategy is based on a screening GCT measuring the glycaemia 1h after ingesting 50g of glucose, followed by a diagnostic OGTT (O’Sullivan test) measuring the glycaemia 0, 1, 2, and 3h after ingesting 100g of glucose [6]. The history of recommendations, showing the gradual progression of the one-step 75g test, is summarised in table 1 [2, 6-8, 10-16, 19-26].
<table>
<thead>
<tr>
<th>Year and organisation</th>
<th>Methods advocated</th>
<th>Pregnancy stage</th>
<th>Threshold values for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1964</strong></td>
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<tr>
<td>O’Sullivan and Mahan  [2]</td>
<td>Two steps: 50 followed by 100g-OGTT</td>
<td>24-33 Weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 0.90 – 1.65 – 1.43 – 1.27* g/L 5.0 - 9.2 - 8.1 - 6.9 mmol/L Whole blood*</td>
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<td><strong>1979</strong></td>
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<tr>
<td>NDDG [7]</td>
<td>Two steps: 50 followed by 100g-OGTT</td>
<td>24-33 Weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 1.05 – 1.90 – 1.65 – 1.45 g/L 5.8 – 10.6 – 9.2 – 8.1 mmol/L Venous plasma **</td>
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<td><strong>1980</strong></td>
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<tr>
<td>OMS [22]</td>
<td>One-step 75 g</td>
<td>24-33 Weeks</td>
<td>75 g : 0 - 2 hours 1.26 - 1.40 g/L 7 - 7.8 mmol/L Venous plasma ***</td>
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<td><strong>1982</strong></td>
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<tr>
<td>Carpenter et Coustan [23]</td>
<td>Two steps: 50 followed by 100g-OGTT</td>
<td>24-33 Weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 0.95 – 1.80 – 1.57 – 1.40 g/L 5.3 - 10.1 – 8.7 – 7.8 mmol/L Venous plasma **</td>
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<tr>
<td><strong>1991</strong></td>
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<tr>
<td>3rd workshop [8]</td>
<td>One-step method (75 g) can replace two-step (50 g then 100 g)</td>
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<td><strong>1996</strong></td>
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<tr>
<td>CNGOF [24]</td>
<td>Two steps: 50 followed by 100g-OGTT</td>
<td>If risk: at first visit, then 24-28, and even 32 weeks No risk: 24-28 weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 0.95 – 1.80 – 1.55 – 1.40 g/L 5.3 - 10.1 – 8.7 – 7.8 mmol/L Venous plasma **</td>
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<tr>
<td>Alfediam [25]</td>
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<td><strong>1996</strong></td>
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<tr>
<td>EASD [10]</td>
<td>One-step 75 g</td>
<td>24-28 weeks</td>
<td>75 g : 0 - 2 hours 1.10/1.45 - 1.63/2.0 g/L 6/8 - 9/11 mmol/L Venous plasma ***</td>
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<td><strong>1999</strong></td>
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<tr>
<td>OMS [12]</td>
<td>Systematic one-step 75 g</td>
<td>24-28 weeks</td>
<td>75 g : 0 - 2 hours 1.05 – 1.40 g/L 5.7 – 7.7 mmol/L Venous plasma ***</td>
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<td><strong>2001</strong></td>
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<tr>
<td>ACOG [26]</td>
<td>Targeted 2 steps 50 followed by 100 g</td>
<td>24-28 weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 0.95 – 1.80 – 1.55 – 1.40 g/L 5.3 - 10.1 – 8.7 – 7.8 mmol/L Venous plasma ** (or NDDG criteria)</td>
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<td><strong>2002-2008</strong></td>
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<tr>
<td>ADA [13-16]</td>
<td>2 steps 50 followed by 100 g, or targeted one-step (75 g)</td>
<td>If high risk: 1st visit then 24-28 weeks If medium risk: 24-28 weeks</td>
<td>100 g : 0 - 1 - 2 - 3 hours 0.95 – 1.80 – 1.55 – 1.40 g/L 5.3 - 10.1 – 8.7 – 7.8 mmol/L** 75 g : 0 - 1 - 2 hours 0.95 – 1.80 – 1.55 g/L 5.3 – 10.1 – 8.7 mmol/L*** Venous plasma</td>
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<td><strong>2008</strong></td>
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<td>NICE [20]</td>
<td>Targeted one-step 75 g</td>
<td>If history of GDM: 16-18 weeks If at risk: 24-28 weeks</td>
<td>75 g : 0-2 hours 1.26-1.40 g/L 7-7.8 mmol/L Venous plasma***</td>
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<tr>
<td><strong>2008</strong></td>
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<tr>
<td>US Task Force [21]</td>
<td>Targeted two-step method</td>
<td>24-28 weeks</td>
<td>100 g : 0-1-2-3 hours 0.95-1.80-1.55-1.40 g/L 5.3-10.1-8.7-7.8 mmol/L venous plasma **</td>
</tr>
</tbody>
</table>

*Values rounded by O’Sullivan, **2 abnormal values for positive diagnosis, ***1 abnormal value for positive diagnosis.
O’Sullivan and Mahan’s historical method in 1964 consisted of a two-step screening (50g GCT followed by 100g OGTT), before the criteria were changed by the American National Diabetes Data Group (NDDG) in 1979 [7].

In November 1991, the 3rd International Workshop on Adverse Perinatal Outcomes in Gestational Diabetes Mellitus proposed that, as recommended by the WHO in 1980, the 75g test should become universal and replace the historical two-step method. The group specified that priority should be given to developing an international consensus on the diagnosis and definition of GDM [8].

In 1992, the International Workshop outlined the importance of taking perinatal outcomes into account, particularly since the evidence available at the time was insufficient to support consensus [9].

In 1996 the EASD recommended the 75g test as an alternative to the 100g test [10].

In 1997, the 4th International Workshop re-iterated its recommendation that the 75g test should replace the 100g test [11].

In 1999, the WHO re-iterated its support to the 75g test [12].

In 2002, the ADA broadened its recommendation to include both the one-step and two-step methods. Both methods remained on offer until 2008 [13-16].

The HAPO study was subsequently set up [17, 18].

In 2007, recommendations from the 5th International Workshop stated that the development of diabetes diagnostic criteria, and correlations between maternal hyperglycaemia and perinatal outcomes should be based on results from the HAPO study [19].

In 2008, the National Institute for Health and Clinical Excellence (NICE) recommended 75 g, with the diagnostic criteria of the WHO, and defined the term as a function of risk factors [20].

In 2008, the United States Preventive Services Task maintained the two-step screening method [21].

6. Common methods used with 50, 75 or 100g glucose loads

6.1. Methods

6.1.1. O’Sullivan screening test (50 g)

The O’Sullivan test involves measuring venous glycaemia 1h after the ingestion of a 50g glucose load, irrespective of whether the woman has eaten or not. It is not necessary to measure fasting glycaemia. If the glycaemia is above a threshold of 1.3 or 1.4 g/L, screening is considered positive and a diagnostic test based on 100g-OGTT will be required. If screening test glycaemia is ≥ 2 g/L, the diagnosis of GDM is positive, with no need for a subsequent OGTT. It is recommended that the delay between the O’Sullivan and diagnostic test should not exceed 7 days to ensure optimal care management.

6.1.2. Diagnostic tests (75 and 100 g)

The OGTT should take place in the morning, after 8-14 h overnight fasting, during which time only water may be ingested. Food intake and exercise levels should remain normal during the three days preceding the test, and smoking is prohibited during the test. If glycaemia cannot be measured straight away, blood should be collected in a tube containing sodium fluoride (6 mg/ml blood), and immediately centrifuged. At room temperature, glycolysis may cause the glycaemia to drop by about 0.4 mmol/L in the first hour, hence plasma should be stored in cool conditions. After collection of a first blood sample, the subject should drink 250-300 ml water containing 75 or 100g of glucose, in less than 5 minutes. Glycaemia is measured before and 2 hours after ingestion for a 75g load, before and after 1, 2 and 3h for a 100g load [12, 27].

The IADPSG recommendations used in the HAPO study were based on the one-step 75g OGTT, with glycaemia measurements at times 0, 1 and 2h [5].

6.2. Reproducibility and diagnostic value of the methods (Table 2)

6.2.1. O’Sullivan screening test (50 g)

In 1993, Espinosa de Los Monteros et al. evaluated the reproducibility of the 50 g test, repeated twice, in 160 women with no prior history of GDM (80 between 12-24 weeks gestation and 80 between 24-28 weeks). The authors examined test reproducibility for three thresholds 1.30 g/L, 1.35 g/L and 1.40 g/L, and found good reproducibility (90%) in non-diabetic women regardless of gestational age. Reproducibility was lower in diabetic women, particularly in the early stages of pregnancy. As a result, the authors recommended testing between 24-28 weeks gestation to ensure optimal reliability [29] (EL2).

6.2.2. Diagnostic test using 100g-OGTT

In 1991, Harlass et al. investigated the reproducibility of the 100 g test, repeated twice, in 64 women at risk for GDM. Diagnostic thresholds were 1.05 – 1.90 – 1.65 and 1.45 g/L after 0, 1, 2 and 3h respectively. Dietary advice and sampling conditions were all identical. Results were reproducible in 78% of cases [29] (EL2).

In 1993, Catalano et al. investigated the reproducibility of the 100 g test, repeated twice, in 38 women at risk for GDM. Diagnostic thresholds were 1.05 – 1.90 – 1.65 and 1.45 g/L after 0, 1, 2 and 3h respectively. Dietary advice and sampling conditions were all identical. Results were reproducible in 76% of cases [30] (EL2).

6.2.3. Diagnostic test using 75 g-OGTT

In 1998, Weiss et al. tested 60 women (30 with and 30 without GDM) first with a 75 g test, then with a randomized
75 or 100g test after 3±1.3 days. Data for all women indicated good reproducibility, and correlation between the two 75g tests was good at 0, 1 and 2h [31] (EL2).

**Reproducibility of the 50g-test is better between 24-28 weeks than between 12-24 weeks of pregnancy. The reproducibility of the 50, 75 and 100 g glucose tests can be rated as good.**

6.3. Are pre-test dietary requirements needed? (Table 3)

Historically, a non-restrictive diet including at least 150 g Carbohydrates (CH) a day was required in the three days preceding an OGTT. This recommendation was based on the 1940 Conn study, showing that the amount of CH ingested before the test had an impact on test results, and that restrictions (<150g CH/day) may increase post-load glycaemia. However, this data concerned only 9 subjects (men and women), including three who were deemed malnourished [32]. Two studies in 1975 and 1999 also suggested that the amount of CH may impact OGTT results. However, both studies included men and non-pregnant women and involved very variable amounts of CH [33, 34]. Only four studies so far have investigated the impact of diet on OGTT results in pregnant women (Table 3).

In 1991, Harlass et al. investigated 37 women with a high risk of GDM randomly assigned to two dietary groups prior to a 100g-OGTT [35].

In 1998, Entrekin et al. compared OGTT results in women who could choose between three types of diet in the three days preceding a 100g-OGTT. The percentage of diagnosed GDM was similar in all three groups (29%, 28% and 28%) [36].

**Table 2**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type and number of women</th>
<th>Test</th>
<th>Results and reproducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espinosa de los Montero et al. 1993 [28]</td>
<td>Prospective 160 women without GDM</td>
<td>2 50g tests 1 day apart 12-24 weeks (n = 80) or 24-28 weeks (n = 80)</td>
<td>If first test is normal: 90% If first test is abnormal 12-24 weeks: 50% If first test is abnormal 24-28 weeks: 83%</td>
</tr>
<tr>
<td>Harlass et al. 1991 [29]</td>
<td>Prospective 64 women at risk*</td>
<td>2 100 g-tests 1-2 weeks apart 24-28 weeks</td>
<td>Reproducibility: 78% 75% of normal results remain normal 3% abnormal (i.e. Positive for GDM) remain abnormal 5% abnormal become normal 17% normal become abnormal</td>
</tr>
<tr>
<td>Catalano et al. 1993 [30]</td>
<td>Prospective 38 women at risk*</td>
<td>2 100 g-tests 1 week apart 24-28 weeks</td>
<td>Reproducibility: 76% 42% normal remain normal 34% positive for GDM remain positive 18% positive become normal 5% normal become positive</td>
</tr>
<tr>
<td>Weiss et al. 1998 [31]</td>
<td>Prospective, randomized 60 women (30 GDM, 30 without GDM)</td>
<td>2 x 75g-test 3 days apart</td>
<td>No difference in 0-1-2h glycaemia between women with and without GDM</td>
</tr>
</tbody>
</table>

GDM = Gestational diabetes mellitus, *women with a glycaemia ≥ 1.35 g/L 1 h after 50 g-load, **Women without known GDM, ***60 women including 30 with and 30 without GDM.

**Table 3**

Data on the influence of dietary requirements prior to OGTT in pregnant women

<table>
<thead>
<tr>
<th>Study design</th>
<th>Population</th>
<th>Dietary requirements</th>
<th>Glucose load</th>
<th>Pregnancy stage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harlass et al. 1991 [35]</td>
<td>37 women at risk* USA</td>
<td>≥ 150 g CH/day for 3 days versus usual diet for a week</td>
<td>100 g</td>
<td>NA</td>
<td>No difference between 0, 1 and 2 and 3 hours glycaemia</td>
</tr>
<tr>
<td>Entrekin et al. 1998 [36]</td>
<td>354 women USA</td>
<td>≥ 150 g CH/day for 3 days or 6 Snicker bars/day or usual diet</td>
<td>100 g</td>
<td>NA</td>
<td>No difference between 0, 1, 2 and 3 hours glycaemia</td>
</tr>
<tr>
<td>Crowe et al. 2000 [37]</td>
<td>20 women at risk** Texas</td>
<td>For 3 days: &gt; 150 g CH/day versus usual diet</td>
<td>100 g</td>
<td>NA</td>
<td>No difference between 0, 1, 2 and 3 hours glycaemia</td>
</tr>
<tr>
<td>Buhling et al. 2004 [32]</td>
<td>34 women, Germany</td>
<td>For 6 days: 50% versus 40% de CH/day</td>
<td>75 g</td>
<td>Ca. 30 weeks</td>
<td>No difference between 0, 1, and 2 hours glycaemia</td>
</tr>
</tbody>
</table>

*(glycaemia > 1.35 g/L 1 h post 50 g), **(> 1.40 g 1 h post 50 g) (greyed-out) OGGT=oral glucose tolerance test, d = days, CH= carbohydrates, NA = Not available.
In 2000, Crowe et al. compared OGTT results in 20 women with a high risk of GDM who followed one of two types of diets in the three days preceding a 100g-OGTT [37].

In 2004, Buhling et al. compared OGTT results in 34 women, where 50% were subjected to a rich CH diet, and 40% to a poor CH diet for the six days preceding a 75g-OGTT [32].

The results of all four studies show that diet type has no effect on OGTT glycaemia results at times 0, 1, 2 and 3h (EL2).

Studies involving pregnant women show that the amount of CH present in the diet for the 3 to 6 days preceding the OGTT has no impact on glycaemia results in OGTT. This finding is true for both 75 and 100g glucose loads and applies to fasting glycaemia, as well as glycaemia after 1, 2 and 3h. There are consequently no indications in favour of a change in diet prior to 75 or 100g-OGTT.

6.4. Is there scope to simplify the 100g-OGTT? (Table 4)

This question arises from the need to compare values obtained with 75 vs. 100g glucose loads. From 1999 to 2006, four studies involved samples of women who were either representative from the point of ethnic background, or carried a high risk of GDM. All studies showed good sensitivity ca. 90%, with 10% of missed GDM diagnosis, when glycaemia values obtained after 3h 100g-OGTT were excluded [38-41].

6.5. Value for money comparison

Many studies show that the two-step GDM diagnostic method is cheaper. In 2010, Meltzer et al. published data from a prospective, randomized study comparing the costs of various one and two-steps diagnostic methods. A total of 1,594 women were randomly assigned to three groups. Group 1: 50g screening test (GCT) followed by 100g diagnostic test (OGTT). Group 2: 50g screening test (GCT) followed by 75g diagnostic test (OGTT). Group 3: 75g diagnostic test (OGTT) only. Basic characteristics were similar in all groups: average age of 31, history of GDM or type 2 diabetes in the family in approximately 41% of subjects, a majority of Caucasians. Costs were respectively 12.57 $ CAN (9.24 EUR)* for the 50g screening test, 36.10 $ CAN (26.53 EUR) for the 75g diagnostic test, and 48.13 $ CAN (35.37 EUR) for the 100g diagnostic test. Data showed that the prevalence of GDM was virtually identical in all three groups (3.7%, 3.7% and 3.6% respectively). Thirty nine percent (7/18) of women who were diagnosed with GDM in group 1, and 61% (11/18) in group 2, had a glycaemia >1.9g/L using the 1h screening test, and required no further testing. This changed the costs to 91.61 $ CAN (68.70 EUR) for the 50g followed by 100g test, 89.03 $ CAN (65.43 EUR) for the 50g followed by 75g test, and 108.38 $ CAN (79.60 EUR) for the 75g one-step test. Therefore this study found the one-step 75g test to be the most expensive [42]. (*EUR cost estimations based on exchange rates in May 2010, 1 Canadian dollar = 0.735 euro). The data presented are based only on a study of a non-French population.

6.6. Venous or capillary glycaemia?

Capillary glycaemia is easier to measure than venous glycaemia and could therefore be seen as the sampling method of choice. However, while many clinicians see capillary glycaemia as acceptable for routine checks in pregnancy, they do not see it as adapted to the screening and diagnosis of GDM. The main limits of capillary glycaemia readings pertain to their precision and to variability between individuals. In 1989, Carr et al. tested four capillary glycaemia readers against venous glycaemia in 84 patients. The standard deviation in

<table>
<thead>
<tr>
<th>Study type and population</th>
<th>OGGT and threshold values</th>
<th>% GDM</th>
<th>% undiagnosed GDM when excluding 3h glycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al. 2006 [41]</td>
<td>Retrospective over 6 years</td>
<td>100g : 0 - 1 - 2 - 3 h</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>6 801 women</td>
<td>0.95-1.80-1.55-1.40 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72% at risk **</td>
<td>18% universal</td>
<td></td>
</tr>
<tr>
<td>Rodacki et al. 2006 [40]</td>
<td>Retrospective</td>
<td>100 g : 0 - 1 - 2 - 3 h</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>65 women with GDM</td>
<td>0.95-1.80-1.55-1.40 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brazilian cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atilano et al. 1999 [39]</td>
<td>Retrospective</td>
<td>100 g : 0 - 1 - 2 - 3 h</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>512 women at risk*</td>
<td>1.05-1.90-1.65-1.45 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Representative cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perucchini et al. 1999 [38]</td>
<td>Prospective</td>
<td>100 g : 0 - 1 - 2 - 3 h</td>
<td>10.2%</td>
</tr>
<tr>
<td></td>
<td>520 women</td>
<td>0.95-1.80-1.55-1.40 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Representative cohort</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OGTT=oral glucose tolerance test; GDM=gestational diabetes mellitus; *glycaemia ≥ 1.40 g/L with 1h, 50 g load; **Women at risk defined by clinical history including risks, positive O’Sullivan test, high fasting or postprandial glycaemia.
Glycaemia was significantly higher using the readers than venous glycaemia [43]. While new generation glycaemia readers have better precision, in 2002, Stahl et al. showed that capillary and venous glycaemia were not interchangeable, and that conversion factors were not precise enough [44]. In 2005, a report from the French National Authority for Health (Haute Autorité de la Santé) highlighted that standard deviations for first generation readers ranged from 6.8% to 8.2% and thus fell short of the acceptable standard of 3.5%. New generation readers do better (2.7% ± 1% standard deviation), but the stability of their precision over time has yet to be proven. In contrast, their accuracy was acceptable, with correlation coefficients ranging from 0.73 to 0.91 [6]. Neither NICE nor IADPSG recommend using capillary glycaemia to screen for or diagnose GDM 5, 20].

Glycaemia should be measured on venous blood samples for diagnostic purposes (outside the scope of self-check follow-ups).

7. Arguments for and against the 75g one-step diagnostic method [45-48]

7.1. Arguments in favour of the one-step method

1. The one-step method is based on a historical method indicated for women with a high risk of developing type 2 diabetes but had been poorly investigated with respect to maternal and foetal complications. The HAPO study now provides robust data on materno-foetal morbidity based on glycaemia values obtained with the one-step method.
2. The one-step method reduces the delay in diagnosis, and therefore the delay in care management.
3. A one-step method could avoid some women missing out on diagnosis. Indeed, three publications show that a proportion of women with abnormal 50g screening test results do not follow-up with the 100g diagnostic test; in 31% of cases for Pima Indian [47], 10% at TriToronto hospital [49], and 23% in New-Zealand [50].
4. The simple criteria of the one-step method are easier to memorise.
5. The one-step takes less time than the two-step method?
6. The one-step method is better tolerated as it induces less nausea (10% failure due to vomiting) [51].

7.2. Argument against the one-step method

The one-step method may be more expensive than the two-step since in 40-60% of cases, GDM diagnosis is confirmed after the 50g-screening test [42]. It is worth noting that this argument is based on a single study and would require more ample confirmation.

8. Alternative methods for the screening of GDM in the second trimester of pregnancy

Owing to the difficulty of performing OGTT, and their poor tolerance by pregnant women, many alternative methods have been suggested for screening and diagnosing GDM, yet none has proven its effectiveness and consequently been endorsed by learned societies.

8.1. Fasting glycaemia between 24 and 28 weeks gestation

Measuring fasting glycaemia (FG) between 24 and 28 weeks gestation may appear as a simple, well-tolerated and cheap way to screen or diagnose GDM, but its use remains controversial for these indications.

8.1.1. Normal FG values in pregnancy

Normal FG values in pregnancy are poorly defined. In the HAPO study, the average FG measured with the 75g-OGTT between 24 and 32 weeks of pregnancy was 0.82 g/L (4.5 mmol/L). However, 50% of patients had an FG < 0.80 g/L (4.4 mmol/L), whereas it was 75% for < 0.85 g/L (4.7 mmol/L) [17].

In a study by Siegmund et al., the glycaemia of 32 Caucasian women 16, 22, 30, 36 weeks gestation and 6 weeks after delivery, was continuously recorded over 3 days using a CGMS (Continuous Glucose Monitoring System). Data showed that average glycaemia tends to increase during pregnancy, with significantly higher values at 36 weeks 0.95 ± 0.09 g/L (5.22 ± 0.5 mmol/L) than at 16 weeks 0.83 ± 0.07 g/L (4.57 ± 0.4 mmol/L). The average FG is stable during pregnancy; 0.82 ± 0.10 g/L (4.5 ± 0.6 mmol/L) at 36 weeks versus 0.79 ± 0.07 g/L (4.36 ± 0.4 mmol/L) at 16 weeks, in contrast to an increasing average postprandial glycaemia: 1.11 ± 0.12 g/L (6.14 ± 0.7 mmol/L) at 36 weeks versus 0.96 ± 0.10 g/L (5.31 ± 0.6 mmol/L) at 16 weeks [52].
8.1.2. Sensitivity (Table 5)

Several studies investigate the sensitivity of FG vs. 75g-OGTT in screening for GDM.

In 1998, Reichelt et al. showed that in 5010 women between 24-28 weeks pregnant, a threshold FG of 0.87 g/L resulted in 88% sensitivity, 78% specificity, 1% positive predictive value (PPV) and 100% negative predictive value (NPV) in screening for GDM [53] (EL2).

In 1999, Perucchini et al. showed that in 520 women between 24-28 weeks gestation, a threshold FG of 0.87 g/L resulted in 81% sensitivity, and 76% specificity. When using the 50g OGC with a 1h-threshold glycaemia of 1.40 g/L, sensitivity was only 59% , and specificity 91% [38] (EL2).

In 2000, Juutinen et al. showed that in 435 women with GDM, a threshold FG of 0.87 g/L resulted in 69.5% sensitivity as a method to retrospectively screen for GDM [54] (EL2).

In 2003, Sacks et al. showed that for 4 507 women in the first trimester of pregnancy (average 10.7 weeks of gestation), a threshold FG of 0.85 g/L resulted in 74% sensitivity, 62% specificity, and a 10% PPV for GDM screening [55] (EL2).

In 2003, Maegawa et al. showed that in 749 women tested twice with the 75g-OGTT, once in the first trimester and once between 24-28 weeks gestation, 2.9% were positive for GDM. Fourteen women (64%) were diagnosed in the first trimester and 8 (36%) between 24-28 weeks. A threshold FG of 0.85 g/L resulted in 75% sensitivity, 90% specificity, and a 17% PPV for GDM screening between 24-28 weeks [56] (EL2).

In 2005, Agarwal et al. showed that in 1685 women between 24-28 weeks gestation, a threshold FG of 0.85 g/L resulted in 78% sensitivity, 32% specificity, and a 22% PPV [57] (EL2).

In 2006, Agarwal et al. compared FG and the 75g-OGTT to screen for DGM in 4258 women between 24-28 weeks gestation. Several reference values were used for the 75 g-OGTT corresponding to guidelines from ADA, WHO, ADPIS, and EASD. When using the WHO and ADA criteria, sensitivity ranged from 70-90%, specificity from 51-53% and PPV from 22-26% for a FG threshold of 0.85g/L [58] (EL2).

Table 5
Sensitivity and specificity of fasting glycaemia as screening test for gestational diabetes mellitus

<table>
<thead>
<tr>
<th>Publication references</th>
<th>Study type</th>
<th>Threshold fasting glycaemia in g/L (mmol/L)</th>
<th>Number of subjects*</th>
<th>Ethnical background</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>Percentage of GDM in the studied population (%)</th>
<th>Reference test and criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichelt et al. 1998 [56]</td>
<td>Prospective Screening</td>
<td>Threshold fasting glycaemia in g/L (mmol/L)</td>
<td>5010</td>
<td>45% Caucasian, 14% African, 41% mixed, 0.4% other</td>
<td>88</td>
<td>78</td>
<td>7.6</td>
<td>75g-OGTT (WHO)</td>
</tr>
<tr>
<td>Perucchini et al. 1999 [38]</td>
<td>Prospective Screening</td>
<td>0.87 (4.8) measured in 75g-OGTT</td>
<td>520</td>
<td>63% Caucasian, 6% African, 19% Asian, 12% other.</td>
<td>81</td>
<td>76</td>
<td>10.2</td>
<td>50 g test followed by 100 g-OGTT (Carpenter and Coustan)</td>
</tr>
<tr>
<td>Juutinen et al. 2000 [54]</td>
<td>Retrospective Screening</td>
<td>0.87 (4.8) measured in 75g-OGTT</td>
<td>435</td>
<td>Finnish</td>
<td>69.5</td>
<td>100</td>
<td>75 g-OGTT 0 - 1 - 2 h 0.87-1.80-1.50 g/L</td>
<td></td>
</tr>
<tr>
<td>Sacks et al. 2003 [55]</td>
<td>Prospective Screening</td>
<td>0.85 (4.7) First trimester</td>
<td>4 507</td>
<td>69% Hispanic, 11.5% African, 10.6% Caucasian, 6.3% Asian, 2.4% other</td>
<td>74</td>
<td>62</td>
<td>6.7</td>
<td>75 g-OGTT 0 - 1 - 2 h 1.0-1.94-1.60 g/L</td>
</tr>
<tr>
<td>Maegawa et al. 2003 [56]</td>
<td>Prospective Screening</td>
<td>0.85 (4.7) measured in 75g-OGTT</td>
<td>749</td>
<td>Japanese</td>
<td>75</td>
<td>90</td>
<td>2.9</td>
<td>50 followed by 75 g glucose loads 0 - 1 - 2 h 1.0-1.80-1.50 g/L</td>
</tr>
<tr>
<td>Agarwal et al. 2005 [57]</td>
<td>Prospective Screening</td>
<td>0.85 (4.7) measured in 75g-OGTT</td>
<td>1 685</td>
<td>90.4% Arabic, 1.5% Indian, 1.5% other</td>
<td>78.1</td>
<td>32.2</td>
<td>19.8</td>
<td>75 g-OGTT (WHO)</td>
</tr>
<tr>
<td>Agarwal et al. 2006 [58]</td>
<td>Prospective Screening</td>
<td>0.85 (4.7) measured in 75g-OGTT</td>
<td>4258</td>
<td>75.5% Arabic, 20.3% Indian, 2% other, 2.3% not available</td>
<td>89.7</td>
<td>69.3</td>
<td>53</td>
<td>14.7</td>
</tr>
<tr>
<td>HAPO 2008 [17]</td>
<td>Prospective Screening</td>
<td>5.1 (0.92) measured in 75 g-OGTT</td>
<td>23 316</td>
<td>48.3% Caucasian, 11.6% African, 8.5% Hispanic, 29% Asian, 2.6% other</td>
<td>51.5</td>
<td>16.1</td>
<td>75g-OGTT 0 - 1 - 2 h 0.92-1.80-1.55 g/L</td>
<td></td>
</tr>
</tbody>
</table>

Se = sensitivity, Sp = specificity, GDM=gestational diabetes mellitus, OGGT = Oral glucose tolerance test, wk= weeks. * In these studies, none of the women were selected on the basis of risk factors for GDM.
In 2008, HAPO study data from over 25,000 patients showed the total incidence of GDM as 16.1%. Isolated measures of FG using a 0.82 g/L threshold within the same population, only detected 8.3% of GDM cases. Taking the 1h-OGTT glycaemia into account increased the percentage of detection to 14%, and adding the 2h-OGTT glycaemia increased it to 16.1% [16]. Hence FG alone failed to detect 49% of GDM, giving a sensitivity of 51% [5, 17] (EL1).

In 1999, Atilano et al. studied 512 women at risk of GDM (50g-GCT glycaemia > 1.40 g/L) retrospectively, including 22% (n=114) presenting with NDDG GDM criteria, and who were subjected to a 2h, 100g-OGTT. Of the 24 women (4.6%) with a FG > 1.05 g/L (5.8 mmol/L), 23 had GDM. The PPV was 96% and the authors proposed to use FG with a 1.05 g/L threshold as a diagnostic method [39] (EL3).

The studies detailed above may be biased since they often involve populations with a high-risk of GDM and results may therefore not apply to lower-risk populations. They are difficult to compare because they are not homogenous and use different tests and diagnostic criteria. They are often carried out for populations with a high risk of GD, thus the results cannot be extrapolated for a population with a lower risk of GD. Finally these studies compare the value of FG against various reference methods to screen for and diagnose GDM, but not to predict the GDM-related perinatal outcomes, which represent the practical side of such evaluations.

8.1.3. International recommendations

The 2001 SIGN (Scotland), and 1996 PNCG (United Kingdom) offer FG as a screening tool for GDM on the first visit in pregnancy, or at 28 weeks of gestation, or in cases where glycosuria is positive [59, 60]. IADPSG recommends FG to screen for unrecognised pre-existing diabetes [5].

Isolated measurements of FG between 24-28 weeks gestation are not suitable to screen for GDM because of poor sensitivity and specificity. When the cut-off threshold for what is considered a pathological result is lowered, sensitivity increases, but specificity decreases. In contrast, measuring FG in the first trimester of pregnancy is a good tool to screen for women with undiagnosed pre-existing diabetes, who are at risk for foetal malformations and materno-foetal complications. Refer to section “when to screen for GDM?”

8.2. Glycosylated proteins

The glycosylation of proteins is an irreversible, non-enzymatic chemical process, which binds glucose to plasmatic proteins. The level of glycosylation is determined by the average glycaemia and exposure time. The use of glycosylated proteins measurements to screen for diabetes remains

<table>
<thead>
<tr>
<th>Publication References</th>
<th>Study type</th>
<th>Threshold HbA1c rate (%)</th>
<th>Pregnancy stage</th>
<th>Number of subjects</th>
<th>Ethnical background</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>Percentage of GDM in the studied population (%)</th>
<th>Reference test and criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefalu et al. 1990 [62]</td>
<td>Prospective Screening</td>
<td>4.6 + 2 SD measured in 100 g-OGTT 26-28 wk</td>
<td>97*</td>
<td>23</td>
<td>87</td>
<td>13</td>
<td>100 g-OGTT (NDDG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puavilai et al. 1993 [64]</td>
<td>Prospective Screening</td>
<td>5.6% measured in 100 g-OGTT 24-28 wk</td>
<td>334*</td>
<td>Indian</td>
<td>66.7</td>
<td>61</td>
<td>7.2</td>
<td>50 followed 100 g loads** 0 - 1 - 2 - 3 h 1.05-1.90-1.65-1.45 g/L</td>
<td></td>
</tr>
<tr>
<td>Agarwal et al. 2001 [65]</td>
<td>Prospective Screening</td>
<td>5.5% and 5% fasting glycaemia 27 wk</td>
<td>430</td>
<td>Arabic, 29.1% Indian, 3.3% other, 1.3% not available</td>
<td>73</td>
<td>66</td>
<td>7</td>
<td>100 g load (Carpenter and Coustan)</td>
<td></td>
</tr>
<tr>
<td>Maegawa et al. 2003 [56]</td>
<td>Prospective Screening</td>
<td>4.8 and 5.8 24-28 wk</td>
<td>749</td>
<td>Japanese</td>
<td>37.5</td>
<td>73</td>
<td>2.9</td>
<td>50 followed by 75 g loads 0 - 1 - 2 - 3 h 1.05-1.30-1.55-1.80 g/L</td>
<td></td>
</tr>
<tr>
<td>Agarwal et al. 2005 [66]</td>
<td>Prospective Screening</td>
<td>&lt; 5.5 and ≥ 7.5 24-28 wk</td>
<td>442</td>
<td>90% Arabic 1.6% Indian 8.4% other</td>
<td>82</td>
<td>21</td>
<td>19</td>
<td>75 g load (WHO)</td>
<td></td>
</tr>
</tbody>
</table>

SD= Standard deviation, Se = sensitivity, Sp = specificity, GDM = gestational diabetes mellitus, OGTT= Oral glucose tolerance test, wk= weeks, * women with risk factors, ** when 1h, 50g-test glycaemia > 1.40 g/L.
controversial. As a GDM screening method, it has only been described favourably in mediocre publications, based on small numbers of populations with a high-risk of GDM.

8.2.1. HbA1c

Several problems are inherent to using HbA1c levels to screen for GDM. Firstly, erythropoiesis increases in pregnancy, causing the erythrocyte population to be younger in pregnant women. Secondly, the time between the start of glucose intolerance and the onset of GDM may be short, making it hard to define a bracket for what constitutes a normal HbA1c rate in pregnancy.

HbA1c levels in pregnancy

In 1994, Loke et al. led a prospective study on 561 mainly Chinese (62.6%) women who were screened using the two-step method (1h, 50 g glycaemia ≥ 1.2 g/L, followed by 75g-OGTT, using WHO criteria) and HbA1c levels. Seventy-two women (12.8%) got a positive GDM diagnosis with the two-step method. The average HbA1c level was significantly different between women who did and did not have GDM: 4.64% (3.66%-5.62%) versus 4.87% (3.73%-6.01%) respectively. However the range of values obtained for each group was so close that it precluded any clinical or diagnostic interpretation [61] (EL2).

In 1990, Cefalu et al. tested 97 women at risk for GDM. Thirteen percent had a positive GDM diagnosis using a 100g-OGTT and NDDG criteria between 26-28 weeks of pregnancy, but there was no significant difference in HbA1c levels between women with or without GDM: 4.6 ± 0.3% versus 4.42 ± 0.2% respectively [62] (EL2).

In 2007, Balaji et al. studied 507 women at various stages in pregnancy, including 155 (30.6%) who were diagnosed with GDM using 75g-OGTT and WHO criteria. The average levels of HbA1c were 6% and 5.3% respectively in women with and without GDM. Regrettably, the authors do not give any detail of the significance of the difference, or of the sensitivity and specificity of the test [63].

Sensitivity

Many studies compare the sensitivity of HbA1c measurements with 75 or 100g-OGTT to screen for GDM. (Table 6).

In the Cefalu et al. study, the sensitivity and specificity of HbA1c levels were 23 and 87% respectively, when using 4.6% + 2 Standard deviations as a threshold, and a 95% upper limit for the confidence interval in the non-GDM population [62] (EL2).

In 1993, Puavilai et al. tested 334 women at high risk of GDM between 24-28 weeks of pregnancy. The average HbA1c level was significantly different between groups with and without GDM: 6.15% (5.74%-6.56%) versus 5.51% (5.42%-5.6%) respectively. The sensitivity of the test in screening for GDM was 66.7%, specificity 61% and PPV 11.8%, using a 5.6% threshold, and 95% upper limit for the confidence interval in the non-GDM population [64] (NP2).

In 2001 Agarwal et al. tested 430 women, including 27% with GDM. Two cut-off thresholds (5 and 5.5%) were considered. With a 5% threshold, sensitivity was 73%, specificity was 66%, and PPV was 44% [65] (NP2).

In 2003, Maegawa et al. tested 749 women, including 2.9% with GDM. Using thresholds of 4.8% and 5.8%, sensitivity was 37.5% and 12.5% respectively, specificity was 73% and 100%, and PPV was 1.8% and 50%. HbA1c levels in the non-GDM population ranged from 4.3 to 5.8%: 4.61 ± 0.27% in the first trimester of pregnancy and 4.56 ± 0.36% in the second trimester [56] (NP2).

In 2005, Agarwal et al. tested 442 women, including 19% with GDM. HbA1c levels were very similar in women with and without GDM. Correlation between HbA1c levels and the results of a 0 and 2h, 75g-OGTT was very poor. With a 5.5% threshold, sensitivity of HbA1c level as a screening test for GDM was 82%, specificity was 21% and PPV 20% [66] (EL2).

8.2.2. International recommendations

No expert group recommends using HbA1c levels to screen for GDM.

IADPSG suggests measuring HbA1c as an alternative method to detect pre-existing diabetes [5].

Few studies investigate the value of HbA1c measurements to screen for GDM and they usually involve small numbers and populations with a high-risk of GDM. Data shows that HbA1c has poor sensitivity as a test, and that levels are very close in women with and without GDM. Such results preclude the use of HbA1c levels as a screening test for GDM. However, HbA1c levels may be a suitable to screen for pre-gestational diabetes.

8.2.3. Fructosamine

Fructosamine is the glycosylated fraction of serum proteins, whose main component is albumin. The half-life of albumin is 19 days, which means that the level of fructosamine reflects the rate of glycosylation over the three weeks preceding the test. Using fructosamine levels to screen for GDM causes several problems. Firstly, there are no established norms for fructosamine levels in pregnancy, and their measurement is not standardised. Secondly, fructosamine levels vary with the level of albumin, which decreases during pregnancy [70].

In 1990, Cefalu et al. (see section on fasting glycaemia) tested 24 women, including 5.2% who had a positive GDM diagnosis using 100g-OGTT between 24-28 weeks gestation (criteria were: 0.9 – 1.65 – 1.45 – 1.25 g/L. vs 0.08 mmol/L versus 1.98 ± 0.02 mmol/L respectively [62].

In 1992, Huter et al. tested 190 women, including 5.2% who had a positive GDM diagnosis using 100g-OGTT between 24-28 weeks gestation (criteria were: 0.9 – 1.65 – 1.45 – 1.25 g/L. vs 0.08 mmol/L versus 1.98 ± 0.02 mmol/L respectively [62].
Average levels of fructosamine were $1.72 \pm 0.25$ mmol/L and $1.6 \pm 0.15$ mmol/L respectively, for women with and without GDM [68]. In 1999 Bor et al. tested 96 women at risk of GDM (1h glycaemia after 50 g-GCT > 1.4 g/L) by using a 100 g-OGTT between 24 and 28 weeks of pregnancy (criteria were 1.03 – 1.89 – 1.64 – 1.40 g/L), and by measuring fructosamine levels. The OGTT diagnosed GDM in 12.5% of women whilst fructosamine levels were similar in GDM and non-GDM patients: $2.05 \pm 0.47$ versus $1.84 \pm 0.29$ mmol/L respectively. The authors also checked that the ratio of albumin/fructosamine was the same in the two groups [67].

8.2.4. Sensitivity (Table 7)

Several studies compared the sensitivity and specificity of using fructosamine levels, or 75g or 100g-OGTT to screen for GDM.

The sensitivity and specificity of the fructosamine test, using a 2.02 mmol/L threshold (95% upper limit of the confidence interval in the population without GDM) in the study by La Cefalu et al. [62] are shown table 7.

In 1990, Nasrat et al. measured fructosamine levels in 170 women, in an effort to determine reference levels throughout pregnancy. Six out of the 98 women at risk of GDM actually developed GDM, and only three had fructosamine levels above the 90th percentile of the reference population for the same gestational stage [69]. In addition, the authors found no correlation between fructosamine levels and birth weight (EL2).

In 1990, Corcoy et al. investigated the screening value of fructosamine levels in 617 women, including 569 without and 48 (8%) with GDM. The threshold fructosamine level was $1.81 \pm 0.13$ mmol/L, based on results obtained in non-GDM women. Of the 48 women with GDM (who had abnormal glycaemia with the 50g-OGTT), only four had fructosamine levels above the threshold [70] (EL2).

In 1995, Uncu et al. studied 42 patients, including 14 with GDM. The sensitivity of fructosamine levels used as screening test for GDM was 71% (using a threshold of 2.85 mmol/L, superior limit of the dosage kit), its specificity was 46% and PPV 40% [71] (EL2).

In 1995, Hughes et al. investigated the value of fructosamine levels to screen for GDM in 682 women. Sensitivity was 79% using a threshold of 215 μmol/L and values corrected for total protein content, specificity was 77% and PPV was 59% [72] (EL2).

In 2000, Weerasekera et al. investigated the value of fructosamine levels to screen for GDM in 210 women. Sensitivity was 87.5% using a threshold of 265 μmol/L. Such results are

<table>
<thead>
<tr>
<th>Publication References</th>
<th>Study type</th>
<th>Threshold fructosamine value</th>
<th>Number of subjects</th>
<th>Ethnical background</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>Percentage of GDM in the studied population (%)</th>
<th>Reference test and criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefalu et al. 1990 [62]</td>
<td>Prospective Screening</td>
<td>2.02 + 2 SD mmol/L measured during 100 g-OGTT 26-28 wk</td>
<td>97*</td>
<td></td>
<td>15.4</td>
<td>97.6</td>
<td>13</td>
<td>100 g-OGTT (NDDG)</td>
</tr>
<tr>
<td>Nasrat et al. 1990 [69]</td>
<td>Prospective Depistage</td>
<td>90th percentile of fructosamine rate in the reference population at the same gestational age for each trimester</td>
<td>98*</td>
<td></td>
<td>50</td>
<td>90</td>
<td>6</td>
<td>75 g-OGTT 0 - 2 h 1.05 - 1.80 g/L</td>
</tr>
<tr>
<td>Corcoy et al. 1990 [70]</td>
<td>Prospective Screening</td>
<td>1.81 ± 0.13 mmol/L</td>
<td>48 with GDM out of 569</td>
<td></td>
<td>8.3</td>
<td>100</td>
<td>8</td>
<td>50 then 100 g loads** (Carpenter et Coustan)</td>
</tr>
<tr>
<td>Uncu et al. 1995 [71]</td>
<td>Prospective Screening</td>
<td>2.85 mmol/L 24-28 wk</td>
<td>42</td>
<td></td>
<td>71</td>
<td>46</td>
<td>33</td>
<td>50 then 100 g loads 0 - 1 - 2 - 3 h 1.05 - 1.90-1.65 - 1.45 g/L</td>
</tr>
<tr>
<td>Hughes et al. 1995 [72]</td>
<td>Prospective Screening</td>
<td>215 μmol/L 210 μmol/L measured during 100 g-OGTT 26-32 wk</td>
<td>682</td>
<td></td>
<td>79</td>
<td>87</td>
<td>77</td>
<td>50 then 100 g loads** 0 - 1 - 2 - 3 h 0.95 - 1.80 - 1.55 - 1.40 g/L</td>
</tr>
<tr>
<td>Weerasekera et al. 2000 [73]</td>
<td>Prospective Screening</td>
<td>265 μmol/L measured during 75 g-OGTT 28 wk</td>
<td>210</td>
<td></td>
<td>87.5</td>
<td>94.5</td>
<td>8</td>
<td>75 g-OGTT 0 - 2 h 1.44-2 g/L</td>
</tr>
<tr>
<td>Agarwal et al. 2000 [65]</td>
<td>Prospective Screening</td>
<td>215 μmol/L 210 μmol/L Fasting rate 27 wk</td>
<td>430</td>
<td></td>
<td>66.3%</td>
<td>29.1%</td>
<td>3.3%</td>
<td>1.3% not available</td>
</tr>
</tbody>
</table>
difficult to evaluate because the reference criteria used to diagnose GDM were high: FG > 1.44 g/L [73].

In 2000, Agarwal et al. (see details of the study in the section on HbA1c) found an 83% sensitivity using fructosamine levels corrected for total protein content and a 215 μmol/L threshold. Specificity was 34% and PPV 32% [65].

8.2.5. International recommendations

There are no international recommendations to use fructosamine levels as a method to screen for GDM.

Studies investigating the value of using fructosamine levels to screen for GDM are often dated and of poor quality. They involve small numbers and populations with a high risk of GDM, and the methods used to measure fructosamine levels are not standardised.

In addition, fructosamine levels tend to be very similar in women with and without GDM, resulting in poor sensitivity. These elements all suggest that measuring fructosamine levels is an unsuitable screening method for GDM.

8.3. Glycosuria

Testing for glycosuria remains compulsory at each antenatal visit. The relevance of this recommendation, which dates back to the time when glycosuria was the sole method available to diagnose diabetes, is now debatable.

Table 8

<table>
<thead>
<tr>
<th>Publication References</th>
<th>Study type</th>
<th>Threshold glycosuria value</th>
<th>Number of subjects</th>
<th>Ethnical background</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>Percentage of GDM in the studied population (%)</th>
<th>Reference test and criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al. 1990 [77]</td>
<td>Prospective Screening</td>
<td>Positive in ≥ 2 determinations ≥ 100 mg/dL (trace)</td>
<td>N = 104</td>
<td></td>
<td>500</td>
<td>27</td>
<td>83</td>
<td>4.4 50 then 100g loads **</td>
</tr>
<tr>
<td>Gribble et al. 1995 [78]</td>
<td>Retrospective Screening</td>
<td>Positive in ≥ 2 determinations ≥ 250 mg/dL (1+)</td>
<td>N = 47</td>
<td>2745</td>
<td>7</td>
<td>98.5</td>
<td>3.1</td>
<td>50 then 100 g loads **</td>
</tr>
<tr>
<td>Hooper 1996 [75]</td>
<td>Retrospective Screening</td>
<td>Positive in ≤ 1 determination ≥ 100 mg/dL (1+)</td>
<td>N = 607</td>
<td></td>
<td>2745</td>
<td>36</td>
<td>98</td>
<td>1.8 0 - 1 - 2 - 3 h 1.05-1.90-1.65-1.45 g/L</td>
</tr>
<tr>
<td>Buhling et al. 2004 [79]</td>
<td>Prospective Screening</td>
<td>Positive (trace, 1+, 2+)</td>
<td>N = 82</td>
<td></td>
<td>912</td>
<td>11</td>
<td>4.1</td>
<td>50 then 75 g loads ** 0 h ≥ 4.95-1 h ≥ 9-2 h ≥ 8</td>
</tr>
</tbody>
</table>

N: Ratio of women with glycosuria/total number of women tested, Se = sensitivity, Sp = specificity, GDM= Gestational diabetes mellitus, OGTT= oral glucose tolerance test.

*Women with risk factors for GDM, ** when 1h, 50g-test glycaemia > 1.40 g/L.
In 1995, Gribble et al. tested 2745 women, including 47 with glycosuria (1.7%). Only six of the 85 (7%) who tested positive for GDM also had glycosuria. The resulting sensitivity of glycosuria as a test for GDM was 7%, and specificity 98.5%. The prevalence of DGM was significantly higher in the group of women with glycosuria than without: 12.8% versus 2.9%, though 8.6% of women without GDM had a positive glycosuria in the third trimester of pregnancy [78] (EL3).

In 2004, Buhling et al. tested 912 women, including 82 (8.2%) with a positive glycosuria. The proportion of women with glycosuria increased throughout pregnancy and was 0.9%, 2.3% and 2.6% respectively in the first, second and third trimester. Thirty of the eighty-two women with glycosuria (36%) had abnormal 50g-screening results, and 4 (4.8%) were diagnosed with GDM. The resulting sensitivity of glycosuria as a test for GDM was 11%, and PPV 6.6%. In addition, 10.8% of the women who tested negative for GDM had positive glycosuria [79] (EL2).

In 2005, Alto et al. published a literature review including four studies investigating the value of glycosuria as a screening test for GDM. Three of the studies have already been cited [77-79], and one study by Hooper et al. involving 607 women, showed that glycosuria had a sensitivity of 36%, 27% PPV and 99% NPV. The authors of the review concluded that testing for glycosuria was an ineffective way of screening for GDM, and that the many false positives led to unnecessary investigations. When the 24-28 week screening for GDM is negative, it is unnecessary to test for glycosuria in the third trimester of pregnancy [75] (EL3).

En 2010, Lawlor et al., studied 1 591 women, including 372 (3.5%) with glycosuria but no pre-existing, or gestational diabetes (however only women with risk factors were screened for GDM). The study showed that women with glycosuria had an increased risk (relative risk of 1.7) of foetal macrosomia, compared to women with negative glycosuria (relative risk of 8.5 for women with pre-existing diabetes and 4.3 for women with GDM) [80].

8.3.2. International recommendations

Glycosuria testing is recommended by many international organisations and countries, such as ADA, Scotland, France and Germany. It is not recommended by NICE or IADPSG [19, 5].

8.4. Random blood glucose test (RBG)

Random blood glucose testing (RBG) has been suggested by some authors to screen for and diagnose GDM. It is a simple and cheap method and has been recommended by the Japanese Diabetes Society [56].

8.4.1. Normal RBG values in pregnancy

In 1984, Lind and Anderson randomly measured the glycaemia in 2 403 women between 28-32 weeks gestation in the two hours following a meal, and after two hours. Average glycaemia was 0.80 ± 0.13 g/L (4.43 ± 0.73 mmol/L) in the two postprandial hours, and 0.74 ± 0.11 g/L (4.11 ± 0.63 mmol/L) after 2h. Thirty-eight women had a glycaemia above the thresholds of 1.11 g/L and 1.0 g/L (6.1 and 5.6 mmol/L) in the two postprandial hours and after 2h respectively. They were subjected to a 75g-OGTT (WHO criteria). Six (15%) were diagnosed with GDM following the OGTT, and the PPV for RBG as a screening test for GDM was 16% [76].

Sensitivity (Table 9)

In 1987, Jowet et al. compared the screening value of the 75g-OGTT with RBG at times 8:00, 12:00, 15:00, 17:00 and 22:00 (meals were at 8:00, 13:00, 17:00) in 110 women with risk factors for GDM. RBG as a screening tool for GDM had 29% sensitivity and 97% specificity at 8:00, when using a 1g/L threshold. In the two postprandial hours, sensitivity was 63% and specificity 82% when using a 1.1g/L threshold, and after the two postprandial hours, sensitivity was 37% and specificity 92% still using a 1.1g/L threshold [81] (EL2).

In 1988, Nasrat et al. investigated the value of RBG to screen for GDM in 250 women. Sensitivity was 16%, and specificity 96% when using a 1.26 g/L threshold in the two postprandial hours and 1.16 g/L after 2h [82] (EL2).

In 1994, Mathai et al. studied 111 women with high risk and 121 women with no risk factors for GDM. The sensitivity of RBG to screen for GDM was 63% using a 0.90 g/L threshold, and specificity was 66% in both populations [83] (EL2).

In 1994, Mc Elduff et al. randomly measured the glycaemia of 714 women. One hundred and fifty seven women whose postprandial glycaemia was > 1.10 g/L or 1h post 50g-GCT was > 1.40 g/L were subsequently tested by 100g-OGTT. Four percent of the women (28/714) had GDM. Measurements of postprandial glycaemia only detected 46% of the women with GDM, and 74% percent (129) of the women with abnormal postprandial glycaemia did not have GDM [84] (EL2).

In 2003, Maegawa et al. (see details of the study in the section on fasting glycaemia) found that RBG had a 37% sensitivity in detecting GDM (using a 0.95 g/L threshold), 82% specificity, and 2.6% PPV [56] (EL2).

In 2007, van Leeuwen et al. studied 1 301 women, including 322 (25%) who had either a random glycaemia > 1.24 g/L, or a 1h post 50g-GCT glycaemia > 1.40 g/L (7.8 mmol/L)
and were subjected to a 75g-OGTT. RBG tests had 14.6% sensitivity in detecting GDM, 89.1% specificity, and 20% PPV [85] (EL2).

8.4.2. International recommendations

- RBG tests are not recommended by Western learned societies for screening GDM, but they are recommended by the Japanese Diabetes Society [56].
- IADPSG recommends RBG as a viable option to detect pre-pregnancy diabetes [5].

**RBG shows poor sensitivity in screening for GDM, which makes it unsuitable in a clinical context. RBG tests are unsuitable to screen for GDM but could be useful to screen for pre-pregnancy diabetes.**

8.5. Fasting and postprandial glycaemia

Measuring fasting and postprandial glycaemia to diagnose GDM appears a simple, cheap and well-tolerated method. Besides it seems more physiological than OGTT. However, few studies have investigated its value in diagnosing GDM.

Value and sensitivity of fasting and postprandial glycaemia in pregnancy (Table 10)

In 1987, Coustan et al. tested 70 women for GDM with a two-step method. Of these, 50 were presumed without, and 20 with GDM based on fasting and postprandial glycaemia results. Of the 24 who tested positive for GDM by OGTT (including 4 out of the 50 women presumed without GDM), 18 had a postprandial glycaemia > 1.20 g/L (6.6 mmol/L). The sensitivity of postprandial glycaemia in screening for GDM was 75% when using a 1.20g/L threshold, and specificity was 94% [86] (EL2).

In 1997, Roberts et al. tested 1038 women, including 102 without, and 936 with risk factors for GDM, using both 75g-OGTT and 2h-postprandial glycaemia. Agreement between the 2h glycaemia in both tests was poor in both groups of women (r = 0.15 et r = 0.35 respectively). Sensitivity and specificity values are shown in table 10 [87] (EL2).

In 2000, Hidar et al. tested 95 women. The sensitivity of postprandial glycaemia as a test for GDM varies according to the selected threshold. The lower the threshold, the higher the specificity, but the lower the sensitivity [88] (EL3).

In 2003, Chastang et al. prospectively tested 354 women between 24-28 weeks gestation, with at least one risk factor for GDM. The reference 50g-GCT was performed, as well as a practical test including fasting glycaemia, and glycaemia 2h after a standard breakfast. When the 1h-50g-GCT glycaemia was > 1.3g/L (4.95 mmol/L), it was followed by a reference
100g-OGTT (Carpenter and Coustan criteria). Results indicated a 20% prevalence of GDM in this population, and agreement between reference and practical tests was 43% when using 0.90 g/L (4.95 mmol/L) and 1.20 g/L (6.6 mmol/L) as thresholds for fasting, and 2h after breakfast glycaemia respectively. The study also measured the sensitivity of both tests in screening for foetal macrosomia. The practical test was more sensitive (47% vs. 16%) than the 100g-OGTT in detecting foetal macrosomia but was less specific (68% versus 80%) [89].

In 2007, Agarwal et al. tested 708 women. The sensitivity of fasting and postprandial glycaemia (thresholds 0.85 g/L and 0.95 g/L) in screening for GDM was 80%, and specificities were 27.5% et 47% respectively [90].

8.5.1. International recommendations

Using postprandial glycaemia measurements to screen for GDM is not recommended by any international organisation.

8.5.2. Conclusion

Few studies investigate the value of measuring postprandial glycaemia as a method to screen for GDM, and threshold values vary between studies. The sensitivity of measuring postprandial glycaemia is poor, and the method is therefore not indicated to screen for or diagnose GDM.

Expert opinion

It is not advisable to use any of the alternative methods such as fasting glycaemia, HbA1c, glycosuria, RBG, or fasting and postprandial glycaemia to screen for or diagnose GDM between 24 and 28 weeks of pregnancy. However, measuring fasting glycaemia in the first trimester of pregnancy may be used to screen for pre-existing diabetes in women with risk factors. Similarly, measuring HbA1c or random glycaemia may be used to screen for undiagnosed pre-existing diabetes.

9. Conflict of interest

No conflict of interest related to the article.

References


